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## **Counterpoint: Is Measuring Sputum Eosinophils Useful in the Management of Severe Asthma? No, Not for the Vast Majority of Patients**

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## Counterpoint: Is Measuring Sputum Eosinophils Useful in the Management of Severe Asthma? No, Not for the Vast Majority of Patients

Quantitating airway inflammation in patients with asthma by noninvasive methods, mainly by enumerating inflammatory cells such as eosinophils in induced sputum, has provided unique information concerning both asthma pathogenesis and the airway response to treatment. Although it is possible for highly specialized centers to reliably induce, process, and quantitate inflammatory cells and markers in sputum,<sup>1</sup> the procedure is time and labor intensive (it takes a skilled coordinator or technician about one-half day), requires meticulous attention to detail, and is expensive (the most expensive procedure done in the Asthma Clinical Research Network of the National Heart, Lung and Blood Institute [NHLBI], except bronchoscopy). Largely for these reasons, a recent meta-analysis concluded that "At present, there is insufficient justification to advocate the routine use of...sputum analysis (due to technical expertise required)...in everyday clinical practice" for tailoring asthma treatment.<sup>2</sup> Although the data discussed in the meta-analysis that support this conclusion should end this debate, the answers to the following five questions provide an additional perspective on this issue.

### QUESTION 1: HOW OFTEN IS SPUTUM EOSINOPHILIA FOUND IN PATIENTS WITH ASTHMA?

In 295 of 377 sputum samples that were acceptable for analysis (those containing <80% squamous cells) from the Wake Forest NHLBI Severe Asthma Research Program site, 35% had  $\geq 2\%$  eosinophils (considered to be elevated by most investigators), whereas 65% (192) had <2% eosinophils (Stephen P. Peters, MD, PhD, FCCP, unpublished data, 2011). Of the 58 patients who met the American Thoracic Society definition of severe asthma,<sup>3</sup> all of whom were on high-dose or inhaled or oral corticosteroids, 43% (25) had  $\geq 2\%$  eosinophils, whereas 33% (78) of the 237 patients with nonsevere asthma (63% on low or medium doses of inhaled corticosteroids) had  $\geq 2\%$  eosinophils (Stephen P. Peters, MD, PhD, FCCP, unpublished data, 2011). Therefore, increased sputum eosinophils are found in a minority, but still a considerable number, of patients with severe and nonsevere asthma, including those on corticosteroid therapy. However, I contend that this cross-sectional

analysis overestimates the proportion of patients with asthma on corticosteroid treatment with elevated sputum eosinophils because the level of adherence to corticosteroid treatment in such studies is unclear.<sup>3</sup>

In the 210 patients randomized in the Asthma Clinical Research Network's Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid (TALC) trial<sup>4</sup> who were treated with low-dose inhaled corticosteroids for a month, had drug adherence estimated to be >80%, but still had inadequate asthma control (they either displayed excess symptoms or had an FEV<sub>1</sub> ≤70% predicted), only 23 (14.4%) had ≥2% sputum eosinophils. I, therefore, suggest that the eosinophilic airway phenotype occurs in a small minority of patients, especially those on corticosteroid therapy in whom adherence has been optimized.

#### QUESTION 2: IS THE EOSINOPHILIC AIRWAY PHENOTYPE STABLE?

In 44 patients with difficult-to-control asthma studied over a 5-year period, 20 patients had ≥2% sputum eosinophils at the first visit and, of those, 14 (70%) had ≥2% sputum eosinophils at the second visit.<sup>5</sup> Ninety-six percent (23 of 24) of patients with asthma without sputum eosinophilia initially were also noneosinophilic at follow-up.<sup>5</sup> Of 40 patients with asthma studied longitudinally at the Wake Forest NHLBI Severe Asthma Research Program site, 24 (60%) changed their classification (eosinophilic [ie, ≥2% sputum eosinophils] to noneosinophilic, or noneosinophilic to eosinophilic) upon subsequent sputum analysis (Stephen P. Peters, MD, PhD, FCCP, unpublished data, 2011). Therefore, I suggest that the eosinophilic airway phenotype is variable over time and not a "stable" phenotype.

#### QUESTION 3: IS THERE AN EFFECT OF SYSTEMIC CORTICOSTEROIDS ON SPUTUM EOSINOPHILIA?

In 11 patients with severe asthma on high-dose inhaled corticosteroids with airway eosinophilia (≥2% sputum eosinophils) who were treated with 120 mg IM of long-acting triamcinolone acetonide, sputum eosinophilia decreased in all patients and reached <2% in 10 of the 11 patients.<sup>6</sup> This was associated with an increase in FEV<sub>1</sub> from 74% to 88% predicted.<sup>6</sup> In 20 patients with severe refractory asthma with sputum eosinophilia, oral prednisone administered at 0.5 mg/kg daily for 2 weeks decreased median sputum eosinophils from 15.5% to 1.1%, and normalized these levels in 11.<sup>7</sup> These changes were

associated with an increase in the mean FEV<sub>1</sub> from 69% to 81% predicted.<sup>7</sup> In the noneosinophilic patients, prednisone did not affect FEV<sub>1</sub>.<sup>7</sup> Therefore, a majority of patients with asthma and eosinophilic airway inflammation will respond to systemic corticosteroid treatment with both a decrease in sputum eosinophils and an improvement in lung function, particularly if the corticosteroid is given intramuscularly.

#### QUESTION 4: DOES MEASUREMENT OF SPUTUM EOSINOPHILS PROVIDE UNIQUE INFORMATION IN ASTHMA TREATMENT?

The data discussed in questions 1 to 3 suggest that an eosinophilic airway phenotype occurs in a minority of patients with asthma, including those on corticosteroid therapy and with severe asthma (although the proportion appears to decrease markedly when adherence to corticosteroid treatment is optimized), that the eosinophilic airway phenotype is often not stable over time, and that systemic corticosteroid treatment either eliminates or decreases markedly the eosinophilic airway phenotype while having a beneficial effect on lung function (FEV<sub>1</sub>).

Although reductions in airway eosinophils are usually associated with improvements in lung function, it is likely that such a positive association does not occur in every individual. (Available data from the published literature do not provide complete information to address this specific issue.) If sputum eosinophilia persists after corticosteroid treatment when there is no change in lung function or asthma symptoms, it could be concluded logically that measurement of sputum eosinophils can provide unique information in a small subgroup of patients with asthma.

#### QUESTION 5: IF SPUTUM EOSINOPHILS PROVIDE UNIQUE INFORMATION ON ASTHMA, WILL YOU ACT ON THAT INFORMATION ALONE, WITH COMPLETE DISREGARD FOR ALL OTHER AVAILABLE INFORMATION?

The answer to this question is the only answer that matters in this debate. Would you, the practitioner, treat sputum eosinophilia in a patient with asthma who has no symptoms, normal lung function, and no exacerbations, just to try to have an effect on the airway eosinophils per se? Conversely, would you fail to provide antiinflammatory drugs to patients without sputum eosinophilia who respond clinically to corticosteroids? I respectfully submit that the answer to both questions is "No."

"Super omnes morbidus." ("Above all else the patient," not the sputum eosinophils.)

Are there any exceptions? Of course, there are always exceptions. If the decision has been made to use an expensive therapy directed specifically against eosinophils (eg, anti-IL-5 agents),<sup>8,9</sup> the presence of airway eosinophilia should be documented by quantitating eosinophils in induced sputum. In published studies, a threshold of 3% has been used as the cutoff to warrant such a treatment approach.<sup>8,9</sup> Although some investigators have argued for measuring blood eosinophils as a surrogate for measuring airway eosinophils in such situations, I would not recommend such an approach. In my experience, these measurements diverge frequently enough (in either underestimating or overestimating sputum eosinophils) as to not be clinically directive.

Finally, this discussion has focused on the role of quantitating sputum eosinophils. Hastie and colleagues<sup>10</sup> have suggested that the presence of both airway eosinophils and neutrophils defines a subgroup of asthmatics at especially high risk of increased asthma morbidity. However, that is a topic for another discussion.

#### CONCLUSIONS

Although quantitating airway eosinophils using induced sputum is necessary for establishing an airway eosinophilic phenotype using current definitions, it has proven value only in defining a patient population suitable for very specific antieosinophil therapies, such as those targeting IL-5. This difficult, time-consuming, and expensive procedure should not be used routinely in the management of patients with asthma, including those with severe asthma. The procedure adds no information that, in and of itself, will alter the therapeutic approach to the patient. However, I do admit that such an approach could provide reassurance to the timid practitioner, who lacks confidence in his/her clinical acumen.

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## Rebuttal From Drs Hargreave and Nair

The conclusions reached by critics of the measurement of sputum eosinophils (and other cell indices), which Dr Peters<sup>1</sup> conveys, misrepresent the facts and are destructive to progress in the assessment and management of severe asthma, which is the focus of this debate. Although severe asthma comprises a minority of patients with asthma, it accounts for a major part of the morbidity and economic burden.

The main criticism is that the procedure is difficult, time consuming, and expensive. This perception results from a failure to recognize what is required to establish a clinical service. Sputum induction is a pulmonary

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